Original Article

Brainstem Auditory Evoked Potential Abnormalities in Type 2 Diabetes Mellitus

Sharat Gupta, Pooja Baweja[1], Shallu Mittal[1], Avnish Kumar[1], Kamal D Singh[1], Raghuvansh Sharma[2]

Departments of Physiology, Gian Sagar Medical College, Ramnagar, [1]Department of Physiology, [2]Internal Medicine, Government Medical College, Patiala, Punjab, India

Abstract

Background: Diabetes mellitus represents a syndrome complex in which multiple organ systems, including the central nervous system, are affected. **Aim:** The study was conducted to determine the changes in the brainstem auditory evoked potentials in type 2 diabetes mellitus. **Materials and Methods:** A cross sectional study was conducted on 126 diabetic males, aged 35-50 years, and 106 age-matched, healthy male volunteers. Brainstem auditory evoked potentials were recorded and the results were analyzed statistically using student's unpaired *t*-test. The data consisted of wave latencies I, II, III, IV, V and interpeak latencies I-III, III-V and I-V, separately for both ears. **Results:** The latency of wave IV was significantly delayed only in the right ear, while the latency of waves III, V and interpeak latencies III-V, I-V showed a significant delay bilaterally in diabetic males. However, no significant difference was found between diabetic and control subjects as regards to the latency of wave IV unilaterally in the left ear and the latencies of waves I, II and interpeak latency I-III bilaterally. **Conclusion:** Diabetes patients have an early involvement of central auditory pathway, which can be detected with fair accuracy with auditory evoked potential studies.

Keywords: Brainstem dysfunction, Diabetes, Diabetic neuropathy, Interpeak latency, Sensorineural hearing loss, Wave latency

Address for correspondence: Dr. Sharat Gupta, Hno# 849, SST Nagar, Rajpura Road, Patiala, Punjab, India. E-mail: sharatgupta29@yahoo.co.in

Introduction

Diabetes mellitus, a chronic multi-systemic metabolic disorder, is fast emerging as an epidemic in both developed and developing countries. The total number of people with diabetes worldwide is projected to rise from 171 million in 2000 to 366 million in 2030. This has been attributed to increasing prevalence of obesity, physical inactivity, population explosion and urbanization. India has the dubious distinction of being the world leader in diabetic population, and according to an estimate, the number of Indians with diabetes is expected to reach 79.4 million by 2030.[1]

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Type 2 diabetes mellitus (T2DM), a subtype of diabetes mellitus, is a chronic metabolic disorder characterized by hyperglycemia, as a result of impaired beta cell function, along with a marked increase in the peripheral insulin resistance, either at the receptor or at post receptor levels, and a rise in the hepatic glucose output.[2,3] Diabetes mellitus has been implicated as an independent causative factor of sensorineural hearing loss.[4] Neuropathy, both central and peripheral, is an important complication of T2DM.[5] Although diabetic neuropathy it manifests clinically much later in the course of the disease, yet its physiological evidence can be obtained much earlier with the help of electrophysiological tests. The electrophysiological testing reflects the bioelectric responses of the nervous system to sensory (somatosensory evoked potentials), auditory (brainstem auditory evoked potentials) or visual stimuli (visual evoked potentials).[6]

Brainstem auditory evoked potentials (BAEP) are the potentials that are recorded in response to brief auditory stimulation to assess the conduction through the auditory pathway, up to the midbrain. BAEPs are

clinically very useful in assessing not only the severity of hearing defects in brainstem dysfunction but also in assessment of hearing in uncooperative patients and children.[7] Typically the BAEPs comprise of five or more waveforms that are recorded within 10 msec of an acoustic stimulus. Wave I originates from peripheral portion of cranial nerve VIII (auditory nerve) near the cochlear nucleus. Wave II originates from cochlear nucleus, wave III from superior olivary nucleus, wave IV from lateral lemniscus and wave V from inferior colliculi in the midbrain.[8] In the recent past, many studies similar to our own have been done worldwide, but the results reported by these, with respect to the BAEP changes in diabetes, have been quite variable.[9,10] Also there is a paucity of data on the BAEP abnormalities in diabetics in India, which is primarily due to the lesser number of studies, which have been done here.

The aim of the present study was to assess the BAEP abnormalities in Indian males suffering from T2DM and to find whether any correlation exists between the observed abnormalities and the fasting blood glucose levels and duration of diabetes or not.

Materials and Methods

The study was conducted in the Department of Physiology in the institute from 2008-2010. The subjects were divided into two groups (i) the diabetic group, and (ii) the control group. The study protocol was approved by the ethical committee of the institute. Written consent was obtained from all the enrolled subjects after explaining them the details of the study in their own language.

The diabetic group comprised of 126 male patients attending the Endocrinology Outdoor clinic of the hospital, while the control group consisted of 106 age-matched male volunteers from among the paramedical and lower staff of the hospital.

Inclusion criteria

Among the first group, those with T2DM, aged 35-50 years and with no past/present or family history of ear diseases or deafness were included. The diagnostic method of T2DM was based on the criteria from the American Diabetes Association.[11] None of the diabetics had a clinically overt neuropathy at the time of study. Among the controls, non-diabetic, age matched males who had no past/present or family history of ear disease or deafness and who were apparently healthy, were included. We did not include subjects over 50 years of age since this age group has an increased incidence of presbycusis, a type of sensorineural hearing loss.

Exclusion criteria

For both the groups, those males were excluded, who had a history of head/ear trauma, significant occupational noise exposure, intake of known ototoxic drugs (e.g., aminoglycosides) or any other medication that might affect normal functioning of the nervous system (e.g., antidepressants, antipsychotics, methyldopa, etc), family history of deafness or any systemic illness that might affect the nervous system (uremia, stroke, hepatic encephalopathy, multiple sclerosis, thyroid disorders, anemia, meningitis, etc), history of tobacco chewing, chronic alcoholism or cigarette smoking, any ear surgery, radiotherapy or chemotherapy. In the control group, in addition to the above criteria, those males were also excluded, who gave a past/family history of diabetes.

Medical and biochemical examination

Prior to the BAEP recordings, all the males were made to undergo the following:

1. Detailed history by way of self administered questionnaires about medical history and lifestyle.
2. Detailed general physical and systemic examination.
3. Complete ENT checkup by way of otoscopic examination and tuning fork tests, to rule out peripheral hearing loss.
4. Serum urea, creatinine and fasting blood glucose (FBG) levels, which were assessed in the clinical biochemistry lab of the hospital.

Brainstem auditory evoked potentials study

It was performed as per the guidelines of the American Clinical Neurophysiological Society.[12] BAEPs were recorded with an evoked potential machine (RMS EMG EP-II Channel, Recorders and Medicare Systems Pvt. Ltd. Chandigarh, India). Before starting the test, age was calculated to the nearest completed year. Standing height without shoes (in cm) and body weight with minimal clothing (in kgs), were also noted. The BAEP recordings were done in a semi-dark room with quiet surroundings. The subjects were made to sit comfortably in a chair, whose back was turned towards the recording machine. The participants were asked to avoid unnecessary movement and to remove all the metallic ornaments that they were wearing. The recording method for BAEP is summarized below:

Monaural stimulation (i.e., one ear at a time), in the form of "broad-band clicks", the acoustic energy of which is spread over a wide range of audio frequencies, was given via headphones at the rates of 11.1 Hz, along with masking of sounds in the contralateral ear. Two thousand clicks were averaged by a filter setting of 100 and 3000 Hz. The clicks were given at an intensity of 60 dB level above the individual perceptual hearing threshold. The latter was estimated by using the ascending and descending

limit method, with increment and decrement intervals of 1dB. Percutaneous silver disc electrodes were used to record the BAEPs. The active electrodes were placed at the left and right mastoid processes (M1 and M2); reference electrode was placed at vertex (Cz position of the 10-20 International system of EEG electrode placement), while the ground electrode was placed on the scalp, in the midline frontal location (Fz position of 10-20 system). Electronic impedance was kept below 5KOhms. Two or more responses were obtained for both the ears separately, to show replicability. The BAEP results were interpreted for the latencies of waves I, II, III, IV, V and Interpeak Latencies (IPL) I-III, III-V and I-V.

Statistical analysis

The data was analyzed statistically by using Statistical Package for Social Sciences version 13.0 (SPSS Inc. Chicago, US). Student's unpaired *t*-test was used for the analysis. Pearson's coefficient was also found between the BAEP waveforms and the duration of the disease and the fasting blood sugar (FBS) levels. The BAEP wave latencies and IPL were dependent variables while both the duration of diabetes and FBG were independent variables.

Results

There was no statistical significance between any of the basic data i.e., age, height and weight of males in diabetes and control groups. However, there was a statistically highly significant difference between the mean FBS levels of both the groups, the values being much higher in diabetic males. In our subjects, the duration of T2DM ranged from 1-15 years [Table 1].

Furthermore, since all corresponding mean BAEP wave latencies are comparable between right and left ear, in both diabetic and control subjects [Tables 2 and 3] thus, it is clear that the right-left latency asymmetry is within normal limits in both these groups.

A comparison between the mean values of the various wave latencies and IPLs was done separately for both the ears, in diabetics and controls [Table 4]. No significant association was found between the latencies of waves I and II in diabetics and controls, with either right ear or left ear stimulation. The latencies of waves III and V were, however, significantly higher in diabetics for both right ear, as well as left ear stimulation. The latency of wave IV was significantly higher in diabetics with right ear stimulation, while it was comparable between diabetics and controls in case of left ear stimulation.

As regards to the interpeak latency comparison, it was seen that while IPL I-III was comparable between both the groups with either right ear or left ear stimulation, the other two measures, i.e., IPL III-V and I-V were both significantly increased in diabetics with both right ear stimulation, as well as left ear stimulation.

Also, all the BAEP wave latencies showed a non-significant positive correlation with both the duration of diabetes and FBG levels [Table 5]. However, there is a stronger correlation of BAEP latencies with FBG levels, as suggested by higher 'r' values, than with the duration of diabetes.

Table 1: Comparison of anthropometric data and fasting blood sugar levels in diabetic and control subjects

Parameter	Diabetics (*n*=126) Mean±SD	Controls (*n*=106) Mean±SD	*P* value
Age (years)	45.7±6.63	46.8±6.11	0.89
Height (cms)	160.1±5.83	160.7±6.95	0.93
Weight (kgs)	66±9.32	64.6±9.21	0.74
FBG (mg/dl)	119.8±16.75	79.5±6.12	<0.001†
Duration of disease (years)	5.68±3.16	NA	NA

**n*: No. of subjects, §NA: Not applicable, †Highly significant (*P*<0.001)

Table 2: Comparison of brainstem auditory evoked potentials latencies (in msec) between the right and and left ear of males with T2DM

BAEP latencies	Right ear Mean±SD	Left ear Mean±SD	*P* value
I	1.64±0.42	1.68±0.38	0.87
II	2.85±0.49	2.90±0.35	0.92
III	3.78±0.53	3.74±0.36	0.27
IV	5.01±0.56	4.92±0.35	1.29
V	5.96±0.68	5.88±0.42	1.33
I-III	2.08±0.29	2.05±0.31	0.34
III-V	2.10±0.72	2.04±0.31	0.39
I-V	4.15±0.71	4.10±0.37	1.26

*None of the differences between any of the latencies is statistically significant (*P*>0.05)

Table 3: Comparison of brainstem auditory evoked potentials latencies (in msec) between the right and and left ear of controls

BAEP latencies	Right ear Mean±SD	Left ear Mean±SD	*P* value
I	1.62±0.15	1.63±0.15	0.89
II	2.79±0.21	2.80±0.19	0.67
III	3.55±0.14	3.53±0.16	0.59
IV	4.84±0.20	4.90±0.18	0.86
V	5.39±0.17	5.46±0.23	1.34
I-III	2.03±0.16	2.00±0.17	0.39
III-V	1.84±0.16	1.82±0.23	0.76
I-V	3.86±0.21	3.83±0.22	1.04

*None of the differences between any of the latencies is statistically significant (*P*>0.05)

Table 4: Comparison of brainstem auditory evoked potentials latencies (in msec) between diabetic and control subjects

BAEP latencies	Diabetic group Mean±SD	Control group Mean±SD	*P* value
Right ear			
I	1.64±0.42	1.62±0.15	0.79
II	2.85±0.49	2.79±0.21	0.06
III	3.78±0.53	3.55±0.14	0.03*
IV	5.01±0.56	4.84±0.20	0.02*
V	5.96±0.68	5.39±0.17	0.01*
I-III	2.08±0.29	2.03±0.16	0.06
III-V	2.10±0.72	1.84±0.16	0.03*
I-V	4.15±0.71	3.86±0.21	0.02*
Left ear			
I	1.68±0.38	1.63±0.15	0.82
II	2.90±0.35	2.80±0.19	0.06
III	3.74±0.36	3.53±0.16	0.03*
IV	4.92±0.35	4.90±0.18	0.93
V	5.88±0.42	5.46±0.23	0.009*
I-III	2.05±0.31	2.00±0.17	0.87
III-V	2.04±0.31	1.82±0.23	0.02*
I-V	4.10±0.37	3.83±0.22	0.02*

*Significant ($P<0.05$)

Table 5: Pearson's correlation coefficient (r) between the brainstem auditory evoked potentials latencies, fasting blood glucose levels and duration of disease in T2DM patients

BAEP latencies	Duration of disease	FBG levels
Right ear		
I	0.012	0.042
II	0.030	0.063
III	0.038	0.192
IV	0.134	0.320
V	0.060	0.030
I-III	0.010	0.199
III-V	0.045	0.327
I-V	0.036	0.186
Left ear		
I	0.019	0.192
II	0.099	0.101
III	0.083	0.012
IV	0.131	0.199
V	0.195	0.327
I-III	0.122	0.320
III-V	0.030	0.118
I-V	0.177	0.210

*All the 'r' values are non significant for both right and left ear ($P>0.05$)

Discussion

The results of our study have shown that the waves III, V and IPL III-V, I-V were significantly delayed bilaterally, while wave IV was significantly delayed unilaterally, in males with T2DM.

Our findings support the results obtained by Talebi *et al*.[13] regarding the significant delay in waves III, IV, V and IPL III-V in patients with diabetes mellitus. Our results also support the findings of Al-Azzawi *et al*.[14] and Gupta *et al*.[15] regarding the significant prolongation of latencies of waves III, V and IPL III-V, I-V in diabetics. However, we did not observe any delay in IPL I-III in diabetics, as reported by both these studies. Our results also support those reported by Durmus *et al*.[16] regarding the significant delay in latencies of waves III and V. However, we also revealed a significant prolongation of IPL III-V and I-V in diabetic subjects, which was not observed by them. The significant rise in latency of wave V and IPL I-V in T2DM patients, as reported by Habib *et al*.[17] and Ren *et al*.[18] was also observed in our study. However, we also revealed a significant rise in latency of waves III, IV and IPL III-V, which were not reported by Habib *et al*.

In the present study, the latency of waves I and II were found to be comparable between both the groups, indicating that the auditory nerve (Cranial Nerve VIII) transmission is normal in males with T2DM. In fact, prolongation of wave I is an inconsistent finding in literature as only a few authors have observed it in diabetic persons.[14,17] On the other hand, the delay in latencies of waves III, IV, V and IPL III-V, I-V which is indicative of a central conduction delay at the brainstem-to-midbrain level, is a more commonly observed finding, as already discussed. The delay in the central conduction time in diabetes may be related to the neurodegenerative changes occurring in these patients. The exact mechanism of neuronal degeneration in T2DM is uncertain. However, as suggested by some recent studies, the insulin resistance in T2DM, not only leads to a compromise in the cell survival, metabolism and neuronal plasticity, but also increases oxidative stress and apoptosis of neurons. Also, an increase in the ceramide generation and a subsequent rise in its trafficking across the blood brain barrier, promotes further insulin resistance and neurodegenerative changes in the brain of patients with T2DM.[19]

In our study, there was a non-significant positive correlation of BAEP latencies with both the duration of diabetes and FBG levels. The absence of a correlation between BAEP latencies and fasting blood glucose in diabetes would appear to rule out subclinical hypoglycemia as a source of delay in the transmission time. Also, the absence of a correlation between BAEP abnormalities and duration of diabetes may be attributed to the relatively shorter duration of diabetes in our patients (mean 5.68 ± 3.16 years). These findings have

been confirmed by many other researchers,[13,16] but a few others have observed a significant correlation of BAEP abnormalities with the duration of diabetes, which may be due to the relatively longer duration of diabetes in their study subjects (mean duration > 10 years).[20,21] Some discrepancies between the results of this study and the ones previously mentioned can be explained by the fact that those studies used a different methodology, as well as different inclusion and exclusion criteria and also studied highly heterogeneous populations.

Keeping in mind the consistent rise in the global incidence of diabetes mellitus and the detrimental effect that it has on the hearing ability of an individual, it is suggested that BAEP testing may also be included in the litany of the routine screening procedures that are of vital importance in diabetes patients (e.g. eye fundus examination, microalbuminuria assessment), wherever it is possible. This is the most important clinical implication of this study.

Study limitations

An important limitation of our study was the use of fasting blood glucose (FBG) as an indicator of the chronic glycemic status of T2DM patients. We admit that FBG values vary on a daily basis, depending upon the glucose levels in blood and are better indicative of acute glycemia. HbA1c is a newer and a better parameter to assess chronic glycemia and long term complications of diabetes. However, due to the higher cost of this test and the poor financial condition of our patients, to which our hospital mainly caters, we were unable to carry out HbA1c testing in our patients. Also keeping in mind the results of many studies, done worldwide including India,[22-24] that have shown a strong, significant positive correlation of HbA1c and FBG levels in diabetics, we feel that FBG could be considered as an equally effective alternative to HbA1c, in the assessment of chronic glycemia.

Another limitation might be the relatively smaller sample size of this study, but this was the maximum number of the participants that we could get, who best fulfilled the study criteria, during the duration for which the study was carried out.

Conclusion

The results of this study clearly suggest that even though earlier on in the course of T2DM, a person might be unaware of any hearing impairment, yet degenerative changes so begin to appear at various levels in the central nervous system. It is possible to detect these subtle neurodegenerative changes, non-invasively and with fair accuracy, at initial stages of the disease itself, by using BAEP studies. Also in consideration of the relative lack of similar studies from the Indian subcontinent, which boasts of an extreme diversity in the socioeconomic status, dietary and lifestyle patterns, there is an urgent need to carry out more such studies on a regional basis in India. This would also help in standardizing the pattern of BAEP abnormalities in diabetes mellitus.

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